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A Causal Analysis of Birth Weight in the Offspring of Monozygotic Twins

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SUMMARY

Data were collected on the birth weights of 1,694 offspring of 385 sets of twins including 108 male and 131 female monozygotic pairs. To resolve the influence of birth order from the genetic, environmental, and maternal effects on birth weight, we analyzed the full-sib and maternal and paternal half-sib correlation matrices for birth orders one to five using a causal model that assumed each live-born child had an influence on the weight of the subsequent birth. Prenatal maternal influences explained 40% of the variation in birth weight of the first-born child and 52% for the fifth child; genetic or environmental factors common to monozygotic twins accounted for 72% of this effect, while environmental variables unique to individual mothers were responsible for the remaining 28%. The inclusion of a birth-order parameter resulted in a highly significant improvement in the goodness of fit of the causal model such that by the fifth child, 46% of the maternal variation could be attributed to the cumulative effects of previous live births.

INTRODUCTION

Maternal effects can arise from systematic environmental factors including those related to birth order, from genetic or cytoplasmic influences of the mother, or from transient environmental circumstances that are unique to a single pregnancy. In the aggregate, maternal effects are recognized to have a more profound influence

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on human birth weight than any other quantitative trait that has yet been analyzed. However, in previous family studies, the effects of birth order have not been fully separated from other sources of variation that contribute to the fetal environment. In the present analysis, we exploit the unique relationships that exist among the offspring of monozygotic twins to achieve an improved resolution of the sources of maternal variation that contribute to differences in the birth weights of normal infants.

MATERIALS AND METHODS

Study Population

Data were collected by interview and questionnaire on the reproductive histories of 385 pairs of adult twins. The sample included data on a total of 1,694 live-born offspring of 108 male and 131 female sets of doubly fertile monozygotic (MZ) twins, as well as 146 like- and unlike-sexed dizygotic (DZ) pairs. A total of 1,613 of the offspring were of birth order five or less. The twins ranged in age from 24 to 75 years of age, and 295 pairs were ascertained from the population-based Medical College of Virginia Twin Registry; data on the remaining 90 pairs were collected in Indiana while the senior author was principal investigator of the Indiana University Human Genetics Center. The information was obtained from female twins and the spouses of male twins and included the birth dates of the parents and offspring as well as the sex, gestational age, parity, birth order (i.e., live births), and birth weight of each live-born child. Whenever possible, the data were verified by medical records, and a formal validation study was conducted in a subset of 102 children.

Methods of Analysis

Means, moments, and Pearson correlations for birth orders of five or less were determined using the SAS statistical package. Causal models were tested by fitting the observed correlations to alternative genetic, maternal, and environmental models whose expectations were derived from the path diagram shown in figure 1. For this purpose, we used a weighted least-squares program developed by one of us (L. J. E.) that incorporates International Mathematical and Statistical Libraries (IMSL) minimization routines. To improve the approximation to normality, observed correlations were transformed to Z values and weighted by their degrees of freedom, while the raw variances were weighted by the inverse of their expected variances. The program provides parameter estimates and their standard errors as well as an overall chi-square test for goodness of fit. The estimated correlations and variances were assumed to be independent in the analysis. Although this assumption is not likely to bias the parameter estimates, it could lead to underestimation of the χ^2 values and standard errors. Analyses based on correlations derived from the following data were compared: gestational-age-adjusted birth weights, and log gestational-age-adjusted birth weights, both classified by birth order, and gestational-age-adjusted birth weight classifed by parity.

RESULTS

Validation Study

The maternal questionnaire responses concerning a subset of 102 infants were compared with data recorded in the hospital record. The observed correlations between the reported and recorded gestational age, birth order, and sex of the infant were .80, .98, and 1.0, respectively. By this criterion, reported birth weight had a validity of .97.

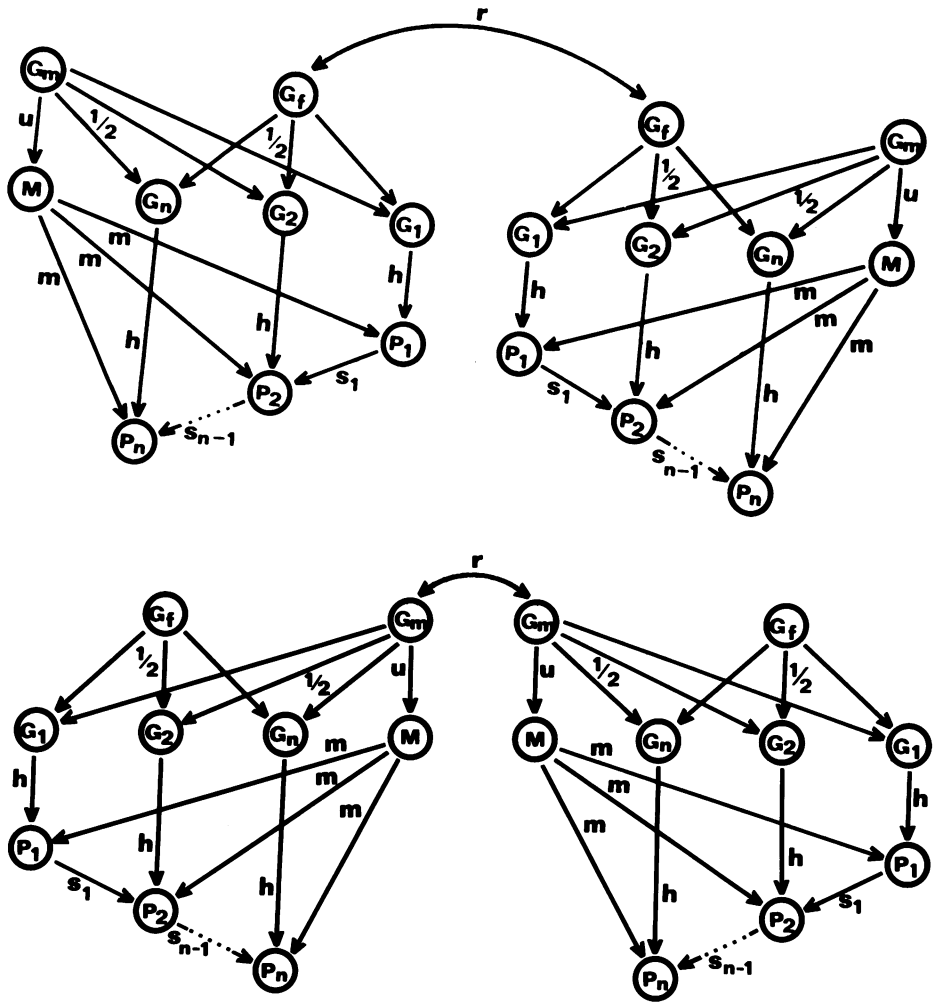

FIG. 1.—Path diagram illustrating postulated causal relationships between birth weights of the offspring of MZ male (*A*, *top*) and female (*B*, *bottom*) twins. G_m, G_f, and G_i are the genotypes of the mothers, fathers, and offspring, respectively, while M is the postulated maternal effect on the offspring birth weights, P_i. The path coefficients from offspring genotype and the maternal effect to the offspring phenotype are h and m, and the extent to which the maternal effects are genetic is measured by u. The path coefficient s_i measures the direct effect of birth weight i on that of offspring $(i + 1)$.

Effects of Sex and Gestational Age

The overall distributions of birth weight by gestational age and sex of the infant are shown in tables 1 and 2. As expected, birth weight increased with gestational age and males were heavier than females ($t = 3.03$, $P < .01$). To remove the effects of variation in birth weight attributable to sex and gestational age, we elected to adjust all of the reported birth weights to those of a 40-week male fetus using the percentile tables for different weeks of gestation that have been published by Lubchenco et al. [1]. The resulting distribution of adjusted birth weights showed no significant departure from normality.

TABLE 1

DISTRIBUTION OF BIRTH WEIGHT BY GESTATIONAL AGE

GESTATIONAL AGE INTERVAL IN DAYS	MALE			FEMALE		
	No.	(Mean, lbs ± SD)		No.	(Mean, lbs ± SD)	
< 238	10	4.70	± 1.34	11	4.07	± 1.09
239–245	6	5.22	± 1.03	4	5.03	± 0.13
246–252	33	5.98	± 1.00	18	5.35	± 0.62
253–259	20	6.43	± 1.28	18	5.97	± 0.95
260–266	49	7.15	± 0.89	44	6.71	± 1.01
267–273	55	7.39	± 1.00	63	7.33	± 0.95
274–280	567	7.53	± 1.07	541	7.42	± 0.99
281–287	78	8.04	± 1.03	70	7.47	± 1.10
290–294	41	8.02	± 0.93	42	7.75	± 1.03
295–301	9	8.41	± 0.81	14	8.11	± 1.27
> 308	0	...	...	1	9.86	...
Total	868	7.46	± 1.18	826	7.29	± 1.15

Effects of Birth Order

The distribution of mean adjusted birth weights for birth orders of five or less is shown in table 3. The mean birth weight increased from birth order one to three and then plateaued, and there was a tendency for later births to exhibit a greater variance than that of the first two children. To examine the effects of birth order on the birth-weight correlations of related individuals, three correlation matrices were calculated. In the first (table 4), the interclass correlations for full-sibling pairs of different birth orders were determined using all of the available data from the families of both the MZ and DZ twin pairs. In the second and third matrices (tables 5 and 6), the pairwise correlations for maternal and paternal half-siblings of different birth order were determined. Inspection of the full-sib

TABLE 2

DISTRIBUTION OF BIRTH WEIGHTS BY SEX OF OFFSPRING

BIRTH WEIGHT (lbs)	MALE		FEMALE		TOTAL	
	No.	%	No.	%	No.	%
< 4.00	4	0.5	4	0.5	10	0.6
4.00–4.49	5	0.6	5	0.6	10	0.6
4.50–4.99	11	1.3	10	1.2	21	1.2
5.00–5.49	25	2.9	35	4.2	60	3.5
5.50–5.99	26	3.0	36	4.4	62	3.7
6.00–6.49	75	8.6	95	11.5	170	10.0
6.50–6.99	114	13.1	120	14.5	234	13.8
7.00–7.49	191	22.0	158	19.1	359	21.2
7.50–7.99	138	15.9	147	17.8	285	16.8
8.00–8.49	115	13.2	102	12.3	217	12.8
8.50–8.99	80	9.2	56	6.8	136	8.0
9.00–9.49	50	5.8	40	4.8	90	5.3
9.50–9.99	19	2.2	9	1.1	28	1.7
10.00–10.49	12	1.4	6	0.7	18	1.1
> 10.50	3	0.3	3	0.4	6	0.4
Total	868	100	826	100	1694	100
Mean ± SD	7.46 ± 1.18		7.29 ± 1.15		7.38 ± 1.17	

TABLE 3

MEANS AND VARIANCES OF ADJUSTED BIRTH WEIGHTS, BY BIRTH ORDER

Birth order	No.	Mean	Variance	SE
1.....	726	7.53	1.07	0.04
2.....	562	7.66	1.03	0.04
3.....	221	7.80	1.10	0.07
4.....	72	7.81	1.38	0.14
5.....	32	7.82	1.34	0.20

correlation matrix revealed a weighted mean correlation of .476 with a tendency for correlations between comparably separated siblings to increase progressively with higher birth orders. Although fewer data were available for the half-sib comparisons, a similar pattern of correlations was seen for both homologous and heterologous birth orders in the offspring of female twins with an overall correlation of .309. In striking contrast, most of the paternal half-sib correlations were low and all were nonsignificant, resulting in a weighted mean of −.031. These findings imply that genetic factors in the fetus have little direct effect on the high correlations between the birth weights of full-siblings and that the effects of birth order on these correlations cannot be entirely attributable to environmental idiosyncrasies that are unique to individual mothers.

Genetic Model

To test these insights, we postulated a causal path model to explain the observed patterns of correlations among full- and half-sibs (fig. 1). The model assumes random mating with additive genetic effects and no dominance, epistasis, X-

TABLE 4

CORRELATION MATRIX OF ADJUSTED BIRTH WEIGHTS FOR 1,613 FULL-SIBS IN 766 NUCLEAR FAMILIES, PARTITIONED BY BIRTH ORDER

	BIRTH ORDER				
BIRTH ORDER	1	2	3	4	5
1.....	1				Symmetric matrix
2.....	.474* (538)	1			$\bar{r}$ = .476 (1,254)
3.....	.367* (206)	0.534* (212)	1		
4.....	.464* (61)	.467* (65)	.566* (67)	1	
5.....	.380† (24)	.617* (27)	.546* (29)	.533* (25)	1
	↓	↓	↓	↓	
Pooled r	.380† (24) Three apart sibs	.512* (88) Two apart sibs	.406* (300) One apart sibs	.499* (842) Adjacent sibs	

NOTE: No. pairs given in parentheses.
* $P < .01$.
† $P < .05$.

TABLE 5

CORRELATION MATRIX OF ADJUSTED BIRTH WEIGHTS FOR 565 MATERNAL HALF-SIB OFFSPRING OF 131 MONOZYGOTIC FEMALE TWINS, PARTITIONED BY BIRTH ORDER

BIRTH ORDER: TWIN 1	BIRTH ORDER: TWIN 2 (NO. PAIRS) 1	2	3	4	5
1	.298* (114)				Symmetric elements pooled $\bar{r}$ = .309 (632)
2	.326* (180)	.238† (75)			
3	.172† (67)	.338* (60)	.337 (18)		
4	.257 (26)	.183 (25)	.396† (26)	.630 (5)	
5	.391 (11) ↓	.642† (10) ↓	.873* (10) ↓	.654 (5) ↓	... ↓
Pooled r	.391 (11) Three apart half-sibs	.362* (36) Two apart half-sibs	.259* (102) One apart half-sibs	.338* (271) Adjacent half-sibs	0.284* (212) Homologous half-sibs

NOTE: No. pairs given in parentheses.
* $P < .01$.
† $P < .05$.

linked gene effects, or genetic environmental interactions. If present, assortative mating would tend to inflate the estimates of additive genetic and maternal effects. However, in the present data, the marital correlation for birth weight in 153 husband-wife pairs was only .08, so that the assumption of random mating is not

TABLE 6

CORRELATION MATRIX FOR ADJUSTED BIRTH WEIGHTS OF 487 PATERNAL HALF-SIB OFFSPRING OF 108 MONOZYGOTIC MALE TWINS, PARTITIONED BY BIRTH ORDER

BIRTH ORDER: TWIN 1	BIRTH ORDER: TWIN 2 (NO. PAIRS) 1	2	3	4	5
1	−.108 (92)				Symmetric elements pooled $\bar{r}$ = −.031 (535)
2	.050 (156)	−.014 (72)			
3	.075 (65)	−.168 (62)	−.022 (19)		
4	−.398 (20)	−.165 (20)	.087 (12)	.227 (3)	
5	−.616 (7) ↓	−.567 (7) ↓	... ↓	... ↓	... ↓
Pooled r	−.616 (7) Three apart half-sibs	−.433 (27) Two apart half-sibs	−.023 (85) One apart half-sibs	−.007 (230) Adjacent half-sibs	−.107 (186) Homologous half-sibs

NOTE: No. pairs given in parentheses.

likely to have introduced a substantial bias into the analysis. Maternal effects are measured by the path coefficient, m, and the extent to which they are determined by genetic or environmental factors common to MZ twins, by u. The direct effect of the fetal genes on birth weight is estimated by the path coefficient h. Finally, each birth is assumed to have an influence on the next by a path whose effect is designated by the coefficient s_i. Depending upon the sign and magnitude of the s_i coefficients, the variance of birth weight may differ with birth order. If genetic models are fitted to the observed correlation matrices, the expected values for the various covariances must therefore be appropriately adjusted by the relevant variances, which may all be expressed in terms of the expected variance of the first-born children, V. The expected values for the variances, the full-sib, and the maternal and paternal half-sib correlations for birth order one to five are as shown in table 7.

Model Fitting

The full model includes eight parameters, s_1, s_2, s_3, s_4, h, m, u, and V, and a total of 40 correlations and five variances are available for their estimation. In the present data set, four correlations for higher birth orders in the half-sib data were lacking, thus reducing the total number of observed statistics to 41. Alternative solutions were fitted to the data by constraining one or more of the parameters to be zero or to assume a fixed value.

As shown in table 8, the null hypothesis that all birth weights had a uniform variance with no covariance between the weights of full- or half-siblings (model 1) was rejected. Among several alternative two-parameter models, one that assumed birth weights are influenced exclusively by genetic or environmental maternal effects that are common to MZ female twins (model 4) could not be rejected and thus provided the most parsimonious explanation for the observed statistics. The inclusion of birth-order effects in model 5 resulted in a highly significant improvement in the goodness of fit ($\chi^2 = 13.24$, 1 df, $P < .001$). No significant improvement was achieved by addition of genetic effects to this solution (model 6), but relaxation of the assumption that the maternal effects are exclusively genetic in origin (model 7) resulted in a further significant reduction of the χ^2 goodness of fit ($\chi^2 = 5.39$, 1 df, $P = .020$). In model 8, separate values of s_i were fitted; their estimated values increased progressively with birth rank, but the evidence for heterogeneity fell short of statistical significance ($\chi^2 = 7.07$, 3 df, $P = .070$). The apparent differences in s_i were not removed by logarithmic transformation of the data (model 8a), and classification of the births by parity gave no improvement in the overall goodness of fit (model 8b).

DISCUSSION

The ability of the mother to constrain the growth of the conceptus regardless of the fetal genotype has obvious survival value. By allowing parents discordant for body size to reproduce freely, the maternal control of fetal growth removes what might otherwise constitute a formidable obstetrical barrier to panmixia. Recognized fetal defects and maternal abnormalities such as diabetic embryopathy can lead to a marked elevation in fetal weight [2]. In other reported families,

TABLE 7

EXPECTED VALUES OF THE PHENOTYPE VARIANCES AND CORRELATIONS

Maternal half-sib	Paternal half-sib	Full-sib
FULL AND HALF-SIB COVARIANCES		
$H_1 = \frac{1}{4}h^2 + m^2u^2 + hmu$	$H_2 = \frac{1}{4}h^2$	$F = \frac{1}{2}h^2 + m^2 + hmu$
Variances		
$V_1 = h^2 + m^2 + e^2 + mhu = 1$	$V_2 = 1 + s_1^2V_1 + 2s_1F$	$V_3 = 1 + s_2^2V_2 + 2s_2(1 + s_1)F$
$V_4 = 1 + s_3^2V_3 + 2s_3(1 + s_2 + s_1s_2)F$		$V_5 = 1 + s_4^2V_4 + 2s_4(1 + s_3 + s_2s_3 + s_1s_2s_3)F$
Full-sib correlations (r)		
$r_{12} = (F + s_1)/\sqrt{VV_2}$		$r_{13} = (F(1 + s_2) + s_1s_2)/\sqrt{VV_3}$
$r_{14} = (F(1 + s_3 + s_2s_3) + s_1s_2s_3)/\sqrt{VV_4}$		$r_{15} = (F(1 + s_4 + s_3s_4 + s_2s_3s_4) + s_1s_2s_3s_4)/\sqrt{VV_5}$
$r_{23} = (F(1 + s_1) + s_2)/\sqrt{V_2V_3}$		$r_{24} = (F(1 + s_1)(1 + s_3) + s_2s_3)/\sqrt{V_2V_4}$
$r_{25} = (F(1 + s_1)(1 + s_4 + s_3s_4)/\sqrt{V_2V_5}$		$r_{34} = (F(1 + s_2 + s_1s_2) + s_3)/\sqrt{V_3V_4}$
$r_{35} = (F(1 + s_2 + s_1s_2)(1 + s_4) + s_3s_4)/\sqrt{V_3V_5}$		$r_{45} = (F(1 + s_3 + s_2s_3 + s_1s_2s_3) + s_4)/\sqrt{V_4V_5}$
Half-sib correlations (t)		
$t_{11} = H_i$	$t_{22} = H_i(1 + s_1)^2/V_2$	$t_{33} = H_i(1 + s_2 + s_1s_2)^2/V_3$
$t_{44} = H_i(1 + s_3 + s_2s_3 + s_1s_2s_3)^2/V_4$		$t_{55} = H_i(1 + s_4 + s_3s_4 + s_2s_3s_4 + s_1s_2s_3s_4)^2/V_5$
$t_{12} = H_i(1 + s_1)/\sqrt{V_4V_2}$	$t_{13} = H_i(1 + s_2 + s_2s_2)/\sqrt{VV_3}$	$t_{14} = H_i(1 + s_3 + s_2s_3 + s_1s_2s_3)/\sqrt{VV_4}$
$t_{15} = H_i(1 + s_4 + s_3s_4 + s_2s_3s_4 + s_1s_2s_3s_4)/\sqrt{VV_5}$		
$t_{23} = H_i(1 + s_1)(1 + s_2 + s_1s_2)/\sqrt{V_2V_3}$		$t_{24} = H_i(1 + s_1)(1 + s_3 + s_2s_3 + s_1s_2s_3)/\sqrt{V_2V_4}$
$t_{25} = H_i(1 + s_1)(1 + s_4 + s_3s_4 + s_2s_3s_4 + s_1s_2s_3s_4)/\sqrt{V_2V_5}$		
$t_{34} = H_i(1 + s_2 + s_1s_2)(1 + s_3 + s_2s_3 + s_1s_2s_3)/\sqrt{V_3V_4}$		$t_{35} = H_i(1 + s_2 + s_1s_2)(1 + s_4 + s_3s_4 + s_2s_3s_4 + s_1s_2s_3s_4)/\sqrt{V_3V_5}$
$t_{45} = H_i(1 + s_3 + s_2s_3 + s_1s_2s_3)(1 + s_4 + s_3s_4 + s_2s_3s_4 + s_1s_2s_3s_4)/\sqrt{V_4V_5}$		

NOTE: The expected variance for first-born children was standardized to unity and used to derive those for later births. In the estimation procedure, the expected variances were multiplied by a scaling constant, V, the true variance of the first born.

TABLE 8

RESULTS OF FITTING ALTERNATIVE CAUSAL MODELS TO GESTATIONAL-AGE-ADJUSTED BIRTH-WEIGHT DATA

MODEL NO.	PARAMETERS								χ^2	df	P	Ho
	V	h	m	u	s_1	s_2	s_3	s_4				
1.....	1.08	...	...	...	...	...	...	...	423.5	40	<.001	$s = u = m = h = 0$
2.....	1.08	.95	...	...	...	...	...	...	73.4	39	<.001	$s = u = m = 0$
3.....	1.08	...	.69	...	...	...	...	...	94.5	39	<.001	$s = u = h = 0$
4.....	1.08 ± .03	...	.65 ± .01	1	...	...	...	...	49.7	39	>.116	$s = h = 0; u = 1$
5.....	1.00 ± .03	.34 ± .13	.56 ± .02	1	.19 ± .04	.19 ± .04	.19 ± .04	.19 ± .04	36.5	38	>.538	$h = 0; u = 1; s_1 = \ldots = s_4$
6.....	1.01 ± .03	...	.39 ± .07	1	.16 ± .04	.16 ± .04	.16 ± .04	.16 ± .04	35.7	37	>.528	$u = 1; s_1 = \ldots = s_4$
7.....	1.03 ± .03	...	.64 ± .03	.84 ± .04	.10 ± .04	.10 ± .04	.10 ± .04	.10 ± .04	31.1	37	>.740	$h = 0; s_1 = \ldots = s_4$
8.....	1.02 ± .03	...	.64 ± .03	.85 ± .04	.06 ± .05	.11 ± .06	.25 ± .08	.28 ± .13	26.0	34	>.834	$h = 0$
8*.....	0.89 ± .03	...	.64 ± .03	.85 ± .04	.05 ± .05	.08 ± .06	.25 ± .08	.23 ± .13	28.2	34	>.764	$h = 0$
8†.....	1.04 ± .03		.67 ± .02	.85 ± .04	.04 ± .04	.00 ± .05	.19 ± .08	.14 ± .13	27.8	34	>.764	$h = 0$

* Log-adjusted birth weight.
† Adjusted birth weight classified by parity.

women have given birth to several extremely large children without obvious cause [3, 4]. It is possible that some familial cases of fetal macrosomy represent genetic defects in this evolutionary adaptation to the pubic arch. At the other extreme, the tendency to bear small-for-dates babies shows clear evidence for recurrence in individuals [5] and aggregation within sororities [6]. Although the exact mechanism is still in doubt, placental insufficiency is considered a likely cause for this phenomenon [7].

In normal infants, the evidence for maternal control of birth weight comes from a comparison of the phenotypic similarities for different classes of relatives. In full-siblings, birth-weight correlations ranging from .26 to .68 have previously been reported [8, 9], adumbrating a major effect on birth weight of either the fetal genes or the intrauterine environment, or both. Robson found a significant correlation of .135 for the gestational age, sex, and birth-order-adjusted birth weights of matrilineal first cousins with a nonsignificant correlation of .015 in cousins related to each other through their fathers [10]. Penrose [11] used these results along with data on the birth weights of twins to attempt a rough partitioning of the causes for variation in human birth weight and concluded that about 18% was attributable to the fetal genotype, 52% to maternal effects, and 30% to unknown environmental causes. However, Penrose made no attempt to actually test the fit of the proposed model with the observed data set, and the twin correlations he utilized were based on pooled observations of unknown chorionicity and placental placement [12], factors that are now known to influence birth-weight correlations in both MZ and DZ twins [13].

In 1955, Morton conducted a genetic analysis of the birth weights in 59,823 pregnancies that occurred in Hiroshima and Nagasaki between 1949 and 1952 [14]. This enormous set of nuclear families included informative data on 30 maternal and 168 paternal half-sib pairs. A significant intraclass correlation of .581 was observed among the former, in contrast to a nonsignificant value of .102 among the latter. Morton's data thus supported previous evidence for a maternal effect on birth weight but gave no indication of its likely origin. Morton also noted that the birth-weight correlation of .523 for adjacent siblings decreased to .425 and .363 for siblings separated by one or two pregnancies, respectively. However, the cross-sectional nature of his data base precluded an effective analysis of the changing correlations between comparably spaced siblings of increasing birth order, leading him to interpret as temporary maternal effects that in retrospect would seem to be more accurately viewed as cumulative influences of increasing birth order. Karn et al. [9] and Donald [8] also examined the birth-weight correlations for siblings of different birth order and found a higher value for the second- and third-born siblings than for the first- and second-born ones. Furthermore, Billewicz [15] reported that exclusion of the first-born child increased the intraclass correlation among remaining siblings, thus contributing to the view expressed by Robson [12] that there may be sources of variation affecting the first child that do not influence subsequent births. In our data, the trend toward higher correlations between siblings of higher birth order appears to extend beyond the first three children, and, if anything, the last two birth orders were more variable than the first two. It thus seems likely that later pregnancies are exposed

to additional sources of variation and that one important influence is the previous reproductive experience of the mother. Finally, analyses of birth-weight data have been reported on the half-sib offspring of identical twins without any attempt to resolve the effects of birth order [16, 17]. These reports support Robson's data in demonstrating that intrauterine environmental factors unique to individual women cannot be the sole explanation for the observed maternal effect on birth weight. They do not, of course, exclude the possibility that environmental factors common to MZ female twins or full sisters may also contribute to these effects.

Our model assumes that the phenotype (birth weight) of each live-born child has a direct effect on that of the next child. The cumulative influences of all previous term pregnancies thus makes the birth weight of a woman's children increasingly predictable at higher birth orders. Since different sources of variation contribute to each birth order, the variances of birth weights may differ with birth order as shown in table 7. When the births were reclassified by parity, a less systematic pattern of correlations resulted that yielded less significant values of s. The birth-order effects thus appear to be attributable primarily to previous term pregnancies, findings consistent with the observation that spontaneous abortions are significantly associated with the birth weight of the previous, but not the subsequent, live-born sibling [18]. Logarithmic transformation of the adjusted birth weights did not substantially alter the evidence for birth-order effects, and all three data sets yielded remarkably similar estimates of m and u.

A summary of the causes for variation in birth weight is given in table 9. For the first child, the fraction of the total variance determined by the maternal effect is given by m^2, of which a proportion u^2 is attributable to genetic or environmental factors common to MZ twins. For subsequent births, the total variance is altered by the influence of previous pregnancies, as shown by the expectations given in table 7. When expressed as a percent of the total variance in birth weight for each birth rank, the magnitude of the maternal effect increased from approximately 41% for the first child to 54% for the fifth child. At all birth ranks, factors

TABLE 9

SUMMARY OF CHANGE IN SOURCES OF VARIATION IN BIRTH WEIGHT WITH BIRTH ORDER (MODEL 8)

COMPONENT OF VARIATION	BIRTH ORDER				
	1	2	3	4	5
Total variance:					
Observed	1.0698	1.0260	1.0984	1.3784	1.3483
Expected	1.0248	1.0792	1.1394	1.3350	1.4257
Maternal effect (%):					
Total	40.6	43.4	45.9	51.5	53.8
Common to MZ twins	(29.3)	(31.3)	(33.1)	(37.1)	(38.8)
Unique to mother	(11.3)	(12.1)	(12.8)	(14.4)	(15.0)
Direct	(40.6)	(38.6)	(36.5)	(31.2)	(29.2)
Through siblings	(0.0)	(4.8)	(9.4)	(20.3)	(24.6)
Specific environment (%):					
Total	59.4	56.6	54.1	48.5	46.2
Direct	(59.4)	(56.4)	(53.4)	(45.6)	(42.7)
Through siblings	(0.0)	(0.2)	(0.7)	(2.9)	(3.5)

common to MZ twins, presumably mostly genetic, accounted for 72% of the maternal variation. The remaining 28% arose from environmental influences that are unique to individual mothers and have a uniform direct effect on all of her children. By the fifth child, nearly 46% of the maternal variation could be attributed to the cumulative effects of previous live births. Finally, although the effects of environmental influences specific to individual births increased with birth order, they accounted for a decreasing proportion of the total variation.

Our genetic model for the determination birth weight describes a particular form of unipolar interaction that may be applicable to other traits, including multiple observations of variables in chronologic sequences where later events cannot possibly influence those occurring at an earlier point in time. Our use of data on the half-sib offspring of monozygotic twins [19] allowed a unique resolution of genetic, maternal, and birth-order effects. Although the analysis of heteropaternal twins [20] would also provide estimates of the correlation between maternal half-sibs with the same parity, this statistic can be obtained for singletons only from the offspring of MZ twins. These kinships are thus of great value for resolving individual and joint parental influences from the complex interactions that can occur among siblings. Other extensions are undoubtedly possible, such as the inclusion of indices measuring the time intervals between births or the effects of specific environmental variables, the joint analysis of birth weight and gestational age, or the inclusion of data on parents, twins, and the offspring of DZ twins in an overall analysis.

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